Marcia Mulkey May 10, 2000
Director
Office of Pesticide Programs

Ms. Mulkey,

On September 9, 1999, I wrote to you expressing my concerns over the August 18, 1999 draft revised cholinesterase policy statement. My August 25 comments directed to that draft are attached. With the assistance of NTEU's Mr. Dwight Welch and Dr. Bill Hirzy, I filed a grievance dated October 6, 1999 in which this draft revised Policy was among the items at issue. Since the filing of that grievance, meetings were held on October 15, 1999 and December 9, 1999 in your office and on November 22, 1999 at Waterside to discuss the grievance. At the October 15 meeting, I had the opportunity, brief though it was, to express to you certain of my scientific concerns, particularly over the use of plasma cholinesterase inhibition as an indicator of toxicity. You advised at that meeting further revisions to the draft would follow, and we would have the opportunity to comment on the same. Accordingly, I have now received for comment a revised draft dated February 28, 2000, and have provided my comments dated March 22. A copy of these comments is also attached.

This is to advise you that based upon my reading of the most recent version of the Policy now being circulated (April 18), I find the paper does not reconcile with my understanding of the many complex scientific issues involved, and in essence is incorrect. The basic concerns expressed in my August 25 and March 22 comments directed to the earlier drafts remain essentially applicable to this more final April version. Given that I consider the cholinesterase Policy now being circulated to be flawed, and in further pursuit of the grievance, my comments offered in this letter and that of September 9 to you, taken in conjunction with my comments directed to the August 18, 1999 and February 28, 2000 drafts constitute my dissenting opinion.

The present Policy paper, like the former drafts, in departing from the original Policy as presented to the SAP (1997) and as published on November 5, 1998 for public comment under FQPA, compromises that which was accomplished by the SAP (1997) *without that Panel's subsequent concurrence or endorsement.* To the extent it thus proclaims new policy, it no longer can affirm the benefit of external peer review, and should not only acknowledge this, but identify those areas of departure.

Perhaps the foremost example of what I mean, because it impinges upon so many of the scientific end points and conclusions in the present Policy statement, is the ignoring of the scientific information in the Background Document (literature review) submitted to the SAP (1997) in support of the original Policy Statement. As you will recall, when SAP (1997) was asked the question, "Does the (literature) review include the major concepts and citations from the literature and present an *overall objective analysis* (emphasis added) consistent with the proposed policy?", the report of the SAP meeting says: "The Panel gave a strongly positive answer", and further along: "Overall, however, the review was judged to comprise an excellent survey of the relevant data, and the Panel was quite satisfied by the review." (p. 19, July 1, 1997 Final Report of the

FIFRA Scientific Advisory Panel Meeting Held June 3-4, 1997). I shall not attempt to recount here the history within OPP of the status of this Background Document, other than to note that you as Director of OPP had restored Part A in the November 5, 1998 publication of the Policy for public comment. As you know I was much pleased with your decision.

Well, Part A has once again been removed from the Policy's Bibliography. Did your staff feel it would go unnoticed, or that some explanation for its removal was not merited, if for no other reason than as a matter of courtesy to its author, given all that has transpired? I have no way of knowing whether its removal was with your concurrence, since I have received no information concerning the matter. I was among persons who officially reviewed the public comments submitted in response to the November 5 offering, and saw nothing that advocated or otherwise would justify its removal. Were there comments I have not seen which would justify its removal? If so, could I be availed of these? I would be pleased to receive some statement of your position on the removal of Part A.

So once again, Part A has been removed, while the Policy's author(s), whomever they may be, endeavor to rewrite the science, and to reach conclusions not in accord with the scientific facts and "overall objective analysis" of the same that received the "strongly positive" and "excellent" endorsement of the outside experts. This constitutes a major issue of compromised due process, and undergirds my claim that the present Policy cannot legitimately claim, as is implied, the benefit or endorsement of an outside panel of experts. It is my understanding that OPP has the prerogative of not following the direction of external peer review panels, but should explain why not when that condition obtains. *The revised Policy should be re-submitted to the same SAP panelists for comment.*

Summary of Scientific Issues of Concern

1) *Plasma cholinesterase inhibition:* The revised draft policy does not ascribe equal importance to plasma and erythrocyte cholinesterase inhibition as surrogates for neural cholinesterase inhibition, as it should, until such time as either has been shown with reliable scientific information to be the better correlate. This was one of the issues I had the opportunity to speak to at the October 15 meeting in your office. At that time, I indicated having presented in the Background Document a number of data sets in which plasma cholinesterase inhibition correlated with neural cholinesterase inhibition on a par with or in a manner superior to that of erythrocyte cholinesterase inhibition. I indicated this occurred with sufficient frequency that one cannot presume that erythrocyte cholinesterase inhibition is superior or preferred in this regard, absent the data in each case to establish the fact. As I recall, you asked Dr. Penny Fenner-Crisp at that meeting whether any survey of data, presumably in OPP's files, had been undertaken to more fully address the question of relative correlation of plasma versus erythrocyte cholinesterase inhibition with neural cholinesterase inhibition. Again, as I recall that conversation, Dr. Fenner-Crisp answered in the negative. ***This question you posed was the eminently appropriate question, residing at the heart of the matter, and should not go unaddressed.*** In drafting the Background Document, I felt sufficient comparative data *was* presented to establish the importance of plasma cholinesterase inhibition, as being on a par with that of erythrocyte cholinesterase inhibition as a correlate of neural cholinesterase inhibition, *in the absence of*

specific data to the contrary in any particular case. That is, the correlation obtains with sufficient frequency that it cannot be discounted absent case by case evidence to the contrary. I might add, this evidence and rationale presented in support of the concept were met with the apparent satisfaction of SAP (1997). So, indeed, until the above question posed by yourself concerning confirmation has been pursued, neither adequate rationale nor acceptable evidence has been presented in the revised Policy to justify altering the position on the use of plasma cholinesterase inhibition as presented to SAP (1997).

In contrast to the Policy as presented to SAP in 1997, the revised Policy *repeatedly* affirms the preference of erythrocyte cholinesterase inhibition over that of plasma cholinesterase inhibition as a surrogate for neural (CNS/PNS) cholinesterase inhibition, while failing to acknowledge this as contrary to the concept that was presented to and endorsed by SAP (1997). Close inspection of the July 1, 1997 report of the SAP meeting reveals the Panel referred frequently to "blood cholinesterase(s)", without indicating erythrocyte cholinesterase inhibition to be "preferred" as is liberally done through out the current Policy paper. This is reflected, for example, in the following text from the SAP (1997) report concerning surrogacy of the inhibition of the two blood enzymes for neural (PNS) cholinesterase inhibition: "Several Panel members noted that the importance of blood cholinesterase values in the regulation of organophosphate and carbamate pesticides has been a point of debate for decades. This conflict might be resolved by comparing the relative sensitivities of acetylcholinesterase inhibition in peripheral tissues to that noted in plasma and erythrocytes. Support for such research could be an excellent investment, since we may need to continue relying on blood cholinesterase values as the only biomarker of exposure/effects in humans. Therefore, more definitive knowledge on the utility of these markers will be essential to provide a sound scientific basis for hazard assessment and regulation." (p. 24) This SAP (1997) philosophy is not reflected in the revised Policy, wherein, for example, it is written: "As explained in Section 3.3, if the measurements of AChE in RBC's are considered methodologically sound, these data generally are preferred over plasma cholinesterase activity as predictors of neural AChE activity, even if the plasma NOAEL/BMD is lower." (Section 4.2) The revised Policy text goes on to say: "However, ..., or the dose response for inhibition of plasma cholinesterase more closely approximates that for AChE inhibition in the nervous system than does the response of RBC acetylcholinesterase inhibition, plasma cholinesterase inhibition may be the more prudent endpoint to use to represent the critical effect." If OPP cannot accept the evidence already presented in the Background Document in support of the use of both enzymes in an equivalent manner absent definitive information to the contrary in a particular case, how would one know which enzyme "more closely approximates that for AChE inhibition in the nervous system" unless he obtains further data, such as by the research activity suggested by SAP (1997) and/or by analyzing the existing data base as implied in your question to Dr. Fenner-Crisp?

The bottom line is that plasma cholinesterase inhibition and erythrocyte cholinesterase inhibition should be considered of equal value, such that the more sensitive responder of the two should be employed in the regulatory setting until such time as proved otherwise on a case specific basis. *OPP should affirm the importance and great value of having two blood borne cholinesterase assays for use in risk assessment given the general lack of adequate neural cholinesterase data*. The implication inherent in the latest draft Policy that OPP gained support from the SAP(1997) for the use of erythrocyte cholinesterase inhibition as "preferred" over plasma cholinesterase

inhibition, is unsubstantiated and regrettable. *Actually, I am here advocating for an **OPP requirement** that relevance be determined on a case specific basis, before any consideration is given to a departure from use of the more sensitive blood enzyme inhibition in risk assessment.*

2) *Low dose effects:* There is considerable published work from peer reviewed literature indicating that following acute or longer term low-level exposures to cholinesterase inhibitors there may result subtle, but clearly important effects, on what I would call behavioral or cognitive performance. Clearly, much additional research is needed in this area. That which I am speaking of is set forth in various sections of the Background Document as presented to the SAP (1997). Now in the February 28 draft Policy statement it is written: *"No credible information exists describing effects following long(er)-term, low-level exposures."* (p. 15), which has been tempered somewhat in the April 18 Policy statement to say rather: *"Little information exists describing effects following long(er)-term, low-level exposures to humans."* Thus with the stroke of the pen, all of the published work cited in the Background Document pertinent to this important subject where the protection of the public health is concerned, is either discredited or ignored; *by whom or on what authority?* There are no authors listed on the revised Policy. Furthermore, no documentation has been presented refuting the works cited in the Background Document, nor the citing of any forum wherein this judgment may have been rendered. Surely support does not derive from the Guideline neurotoxicity studies (excepting developmental neurotoxicity which is in its infancy in terms of data accumulation), which do not even incorporate assessments of effects on such parameters as learning or memory, or other cognitive performances. When the Background Document was completed, my Branch Chief at that time spoke favorably of the work, and we agreed we would respond to any science based criticism of the science involved. We also agreed we would not accept unsubstantiated or undocumented criticisms. The above quote from the most recent draft Policy statement simply wipes away, without offering any countering rationale, the work of many scientists cited in the Background Document, which Document I reiterate was graced with favorable comments from the SAP (1997) panelists, themselves experts in the field.

3) *FQPA issues:*

a) The draft Policy does not address the role of cholinesterase inhibition in evaluating the susceptibility (child versus adult sensitivity) issue required under FQPA. The Policy refers to yet another Policy that deals with the implementation of FQPA, but neither does that document concern assessments of cholinesterase inhibition. So no directive is found in the Policy toward a need for the assessment of inhibition of cholinesterase, the enzyme organophosphates and carbamates by design inhibit, in the young/developing individual versus adult to address susceptibility under FQPA, even though such information may well be the most sensitive in characterizing comparative responses.

b) The November 5, 1998 public comment offering of the cholinesterase Policy was designed in part to deal with FQPA. Among questions posed for public comment were: #5: "Should comparative data on ChEI in the young exposed pre-natally, during infancy (nursing), and during childhood be considered essential for defining the relative sensitivity of the young and adults?" and #6: "Are other measures, such as functional measures or clinical signs, or learning and

memory, similarly important?" Yet, although the cholinesterase Policy references the 1998 publication of the Policy for purposes of public comment, it does not mention, even so briefly, the results of these particular endeavors. That which should be briefly referenced in the Policy in relation to FQPA with respect to these two very important questions can be found in HED's April 9, 1999 draft report entitled: The Agency's Responses to Public Comments on the Draft FQPA Science Policy Document: Office of Pesticide Programs Science Policy on the Use of Cholinesterase Inhibition for Risk Assessments of Organophosphate and Carbamate Pesticides: "There is a growing literature on the effects of early exposures on cholinesterase inhibition and neurobehavioral measures. In more recent developmental neurotoxicity studies, cholinesterase inhibition has been assessed in both dams and offspring, as well as the variety of functional tests, including learning and memory tasks, that are included in that guideline. While the larger issues of the scope of requirement of developmental neurotoxicity studies or other related studies are beyond the scope of this review of cholinesterase policy, for cholinesterase inhibitors, measures of cholinesterase inhibition and assessment of cholinergic functions (which includes learning and memory) are specifically appropriate and important to the evaluation of these classes of chemicals." (p. 21)

c) In the August draft Policy, the claim was made that most studies contain cholinesterase data. However, since I noted in my comments to that draft that cholinesterase data is not obtained in reproduction and developmental toxicity studies, those very studies relied upon most heavily to address the relative susceptibility between young/developing individuals and adults, the claim has been removed from the recent draft. In my view, the preferred course would have been to acknowledge that cholinesterase data is not obtained in these studies, and that this constitutes a fundamental weakness in the data base toward obtaining *complete* and *reliable* data for the protection of infants and children as required by Congress under FQPA.

d) In the earlier draft, the so called "blood-brain barrier" was noted as being important in protecting the CNS from the effects of xenobiotics. Yet, once I noted in my comments (and perhaps others in their comments as well) that this protective interface may be poorly developed in younger individuals leaving them more vulnerable than adults, it was removed from the Policy. Rather, in my view, the text should have been embellished to reveal the concern, particularly as this relates to the obtaining of *reliable* data under FQPA.

Recommendations

a) Since substantial revisions to the cholinesterase Policy have been made following the SAP (1997), the variations existing with respect to the Policy as presented to Panel of experts should be summarized and submitted for their comment and possible endorsement.
b) The Policy should note and justify departures from those conclusions and opinions rendered by the 1997 SAP.

c) As a conservative public health policy, there should be affirmation in the Policy of reliance upon both plasma and erythrocyte cholinesterase inhibition, whichever is most sensitive, until established otherwise.

d) The Policy should note the advantages in having two blood enzyme assays, given the various deficiencies in obtaining reliable neural cholinesterase data, while explaining what may be problematical (or so negative) about relying on the more sensitive of the blood enzymes.

e) To the extent the Policy adheres to a *preference* for erythrocyte cholinesterase inhibition versus that in plasma, more support for this philosophy is needed in the paper than the observation that erythrocyte and neural cholinergic cholinesterases are acetylcholinesterases.

f) OPP should institute a review of cholinesterase data in its files to determine whether it can be concluded that erythrocyte cholinesterase inhibition is to be *preferred* over plasma cholinesterase inhibition as a surrogate for neural cholinesterase inhibition, as a general and abiding principle.

g) The Policy should acknowledge the published works in the Background Document that reveal adverse effects following longer term low level exposures to cholinesterase inhibiting compounds, while affirming the importance of and recommending further research in this area.

h) The Policy should note the importance of obtaining comparative cholinesterase data in young/developing individuals versus adults and in obtaining behavioral effects data (e.g. developmental neurotoxicity testing) in order to address requirements for *reliable* and *complete* data as mandated by Congress under FQPA.

i) The Policy should acknowledge Parts A and B of the Background Document in the Policy's Bibliography.

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